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*Letters in Organic Chemistry*, Year, *Volume* 

# Diastereoselective Synthesis of Nitropyrrolizidines from Enantiopure *exo*-4-Nitro-3,5-diphenylproline through 1,3-Dipolar Cycloadditions of non-Stabilized Azomethine Ylides

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*Dedicated to Prof. Miguel Yus on the occasion of his 70th birthday and for his contribution as Editor-in-Chief of Letters in Organic Chemistry*

**Abstract:** Enantiopure *exo*-4-nitro-3,5-diphenylproline reacts with aldehydes and electrophilic alkenes, in good yields, through a multicomponent 1,3-dipolar cycloaddition where the intermediate azomethine ylide is generated by the decarboxylative route. The reactions with maleimides afford diastereoselectively nitropyrrolizidines. Dimethyl fumarate and 1,2-bis(phenylsulfonyl)ethylene also give variable mixtures of diastereoisomeric nitropyrrolizidines. The replacement of aldehydes by phenyl-3-buten-2-one also affords satisfactory results with high diastereoselection although in lower yields. The stereochemical outcome is studied and defined according to the absolute configuration of the resulting cycloadducts.

**Keywords:** pyrrolizidine · nitroprolinates · cycloaddition · azomethine ylides · decarboxylation · multicomponent.

## 1. INTRODUCTION

Pyrrolizidine alkaloids (PAs) constitute one of the most attractive families of natural products [1] due to their wide and diverse set of biological applications. However, hepatotoxicity, especially veno-occlusive disease, is the most serious result of ingestion of PAs [2,3]. On the other hand, PAs are not all toxic and the range of potential activity is very promising in many scientific areas [4]. Although the most abundant are hydroxylated PAs, non-hydroxylated natural pyrrolizidines shown in Figure 1 also exhibit potent glycosidase inhibition apart from other biological properties [5].

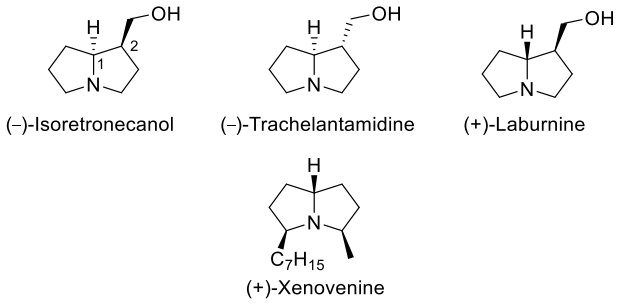


**Figure 1.** Non hydroxylated naturally occurring PAs.

There are several approaches to the synthesis of these alkaloids [1,6] but the most straightforward route consists in the employment of 1,3-dipolar cycloaddition (1,3-DC) of alkenes and stabilized azomethine ylides generated from prolinates, following the typical iminium route (Scheme 1, eq. a) [7,8], or even following a generation of non-stabilized azomethine ylide through a decarboxylative route employing proline (Scheme 1, eq. b and c). This last route allowed the synthesis of complex skeletons when proline and isatine were involved in the process [9] In this sense, Felluga *et al*. also described a three component decarboxylative diastereoselective 1,3-DC version using (2*S*,4*R*)-4-hydroxyproline and 2,3-butanedione or ethyl pyruvate with β-nitrostyrene to give, at room temperature, mixtures of diastereomeric pyrrolidines in good yields (78-90%) (Scheme 1, eq. c). [10]

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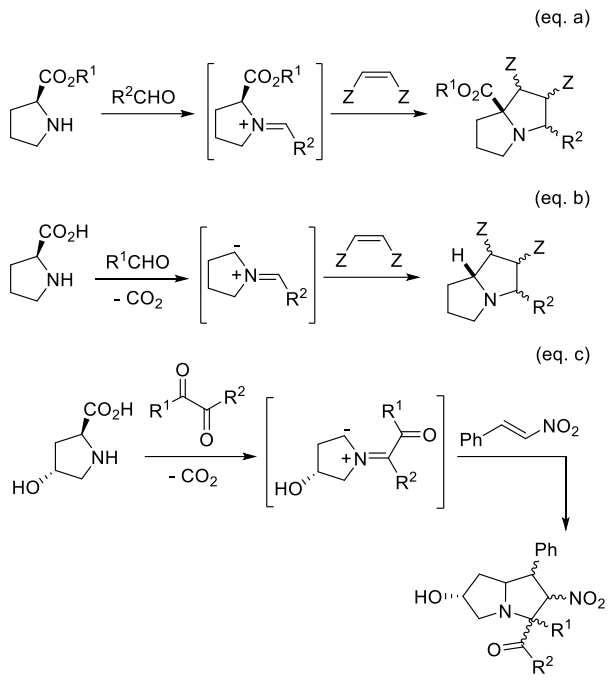
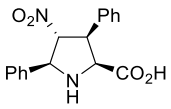



**Scheme 1**. Pyrrolizidine synthesis from azomethine ylides generated by the iminium route or by decarboxylation of proline derivatives.

To the best of our knowledge, this is the sole publication in which a chiral proline derivative was employed for the preparation of pyrrolizidines. So, according to our experience in the preparation of enantiomerically enriched pyrrolizidines, following the route depicted in eq. a) of Scheme 1 from enantiomerically enriched prolinates [7c], we decided to study the diastereoselective multicomponent decaboxylative 1,3-DC using enantiomerically pure nitroprolinate *exo*-**1**, aldehydes or ketones and electrophilic alkenes. So, the synthesis of polysubstituted non-hydroxylated pyrrolizidines will be surveyed.

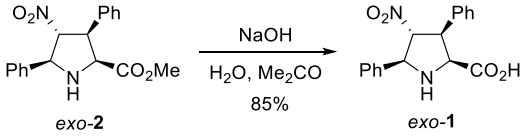


*exo*-**1**

The selection of this starting pyrrolidine **1** bearing a nitro group [11] is due to the recent importance of nitroprolinates as useful tools in organic synthesis as organocatalysts [12,13,14], chiral ligands [12,15,16], and chiral building blocks [17,18]. Their biological properties are very interesting: for example, it was found a family of inhibitors of $\alpha_4,\beta_1$-integrin-mediated hepatic melanoma and in a murine model of colon carcinoma metastasis, as well as potent antiadhesive properties in several cancer cell lines [19,20]. Several compounds acted as inhibitors of skin cancer [21], they can increase the mortality of zebrafish embryos [22], and a series of nitroprolinates were successfully tested as antimycobacterials against M. tuberculosis H37Rv strain [23,24,25]. Besides, the nitro group can be easily transformed in several functional groups and it has been found as the responsible atomic arrangement of stereodivergent cycloaddition processes [18].

## 2. RESULTS AND DISCUSSION

Enantioenriched methyl 4-nitro-3,5-diphenylprolinate (*exo*-**2**), prepared by enantioselective catalytic 1,3-DC of methyl benzylideneglycinate with β-nitrostyrene, in the presence of a chiral phosphoramidite·AgOBz complex (5 mol%) in >99:1 er (>99:1 *exo*:*endo* dr) [26,27], was allowed to react through a hydrolytic process (Scheme 2). Proline derivative *exo*-**1** was obtained in 85% yield by treatment with sodium hydroxide in a 1:1 water:acetone [14] solution at room temperature during 16 h.




*exo*-**2** *exo*-**1**

**Scheme 2**. Synthesis of proline derivative *exo*-**1**.

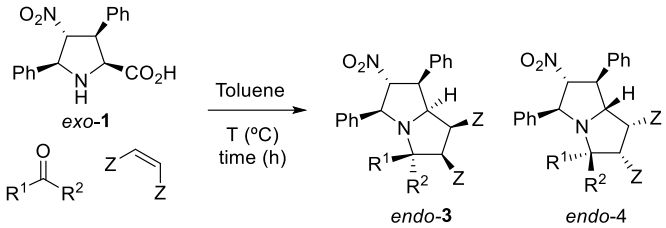
Next, the multicomponent 1,3-DC between nitroproline *exo*-**1**, cinnamaldehyde and *N*-methylmaleimide (NMM) was studied (Scheme 3, Table 1). Toluene was selected as solvent because it was the most appropriate in previous articles regarding [3+2] [7b,c] or [4+2] [18] cycloadditions involving prolinates. Temperature was the main parameter to be implemented for achieving the maximum conversion. The decarboxylation of the iminium salt formed between *exo*-**1** and cinnamaldehyde occurred at room temperature as well as the successive cycloaddition with NMM (Table 1, entry 1). In this case, a mixture of diastereoisomers *endo*-**3a**:*endo*-**4a** was obtained in 40:60 ratio and in excellent 90% overall yield. The conversions of this reaction decreased when lower temperatures (10 °C or 0 °C) were assayed. *N*-Phenylmaleimide (NPM) was tested under the same reaction conditions affording a 1:1 mixture of inseparable *endo*-**3b** and *endo*-**4b** adducts in 81% overall yield (Table 1, entry 2). However, when *N*-(5-bromophenyl)maleimide was used a total diastereoselection was observed after analyzing the $^1$H NMR spectra of the crude material. Product *endo*-**3c** was isolated in 80% yield (Table 1, entry 3).

Dimethyl fumarate was found to be an appropriate dipolarophile because total diastereoselection was observed giving *endo*-**3d**. The temperature of the multicomponent sequence was 25 °C as well, in short reaction time (6 h) and in good 76% yield (Table 1, entry 4). A similar chemical yield was achieved when 1,2-bis(phenylsulfonyl)ethylene (BPSE) was employed as dipolarophile under the same reaction conditions, but the diastereoselection was lower obtaining an 70:30 mixture of presumed *endo*-**3e**:*endo*-**4e** and *endo*-**3e** could be isolated in 50% yield allowing the configuration assignment (Table 1, entry 5).

When other aldehydes, different to cinnamaldehyde, were studied, namely benzaldehyde or dihydrocinnamaldehyde, longer reaction time (17 h) and higher temperature (70 °C) were needed. The diastereoselection of the reaction with different dipolarophiles regarding benzaldehyde and dimethyl

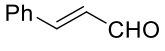
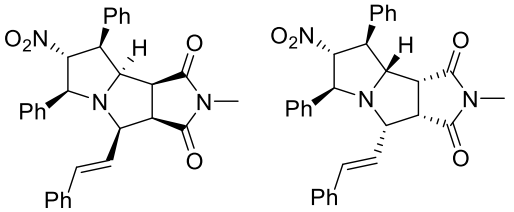
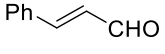
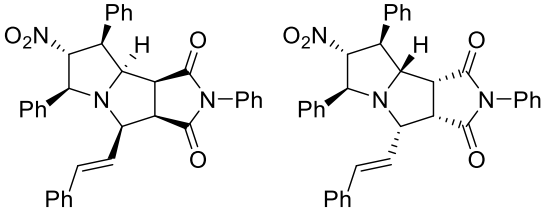
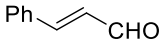
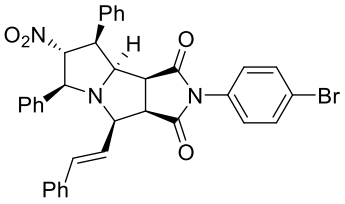
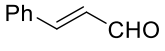
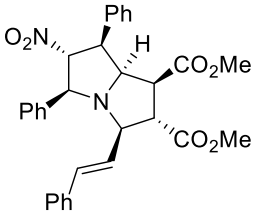
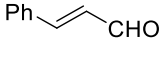
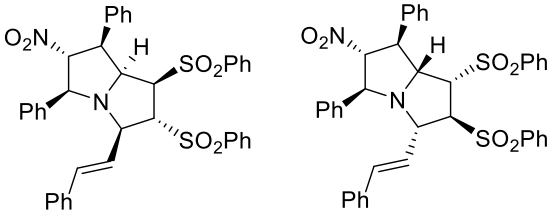
fumarate was very low obtaining a 66:34 *endo*-**3f**:*endo*-**4f** ratio in 84% overall yield (Table 1, entry 6). In both examples performed with dihydrocinnamaldehyde 65:35, inseparable mixture of the corresponding products *endo*-**3g**:*endo*-**4g** and *endo*-**3h**:*endo*-**4h** were isolated in 23% and 26% overall yields, respectively (Table 1, entries 7 and 8).

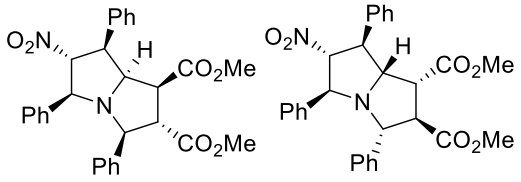
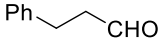
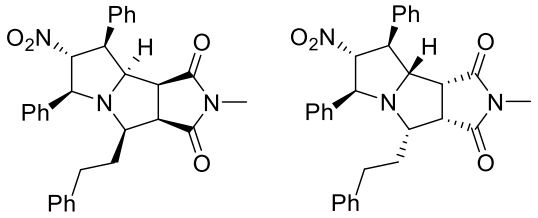
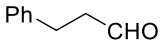
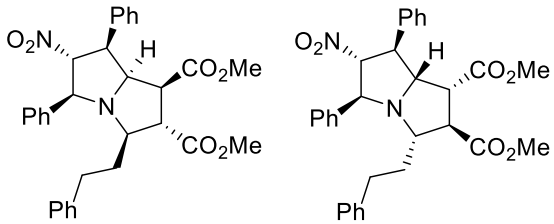
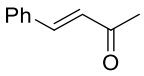
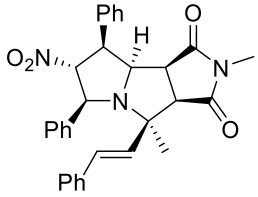
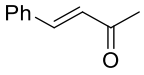
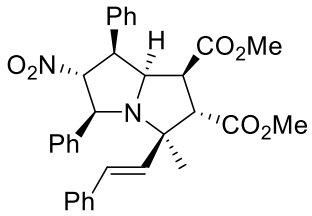
4-Phenyl-3-buten-2-one also formed a reactive azomethine ylide after decarboxylation, ready to react with NMM and dimethyl fumarate (Table 1, entries 9 and 10). The highest both diastereoselection and chemical yield was obtained with NMM (only *endo*-**3i** was isolated, 47% yield) meanwhile dimethyl fumarate furnished an unpurified pyrrolizidine *endo*-**3j** in 30% yield.




**Scheme 3**. Multicomponent diastereoselective 1,3-DC with *exo*-**1**, aldehydes/ketones and dipolarophiles.

**Table 1.** Synthesis of nitropyrrolizidines *endo*-**3** and *endo*-**4**.

| Entry | $R^3$-CO-$R^4$ | Dipolarophile | time (h) | T (°C) | Product Structure, Ratio, Yield (%) [a] |
|---|---|---|---|---|---|
| 1 |  | NMM | 6 | 25 |  *endo*-**3a** (36%) *endo*-**4a** (54%) |
| 2 |  | NPM | 6 | 25 |  *endo*-**3b** (50: 50) *endo*-**4b** (overall 81%)[b] |
| 3 |  | N(4-Br-)PM | 6 | 25 |  *endo*-**3c** (80%) |
| 4 |  | Dimethyl fumarate | 6 | 25 |  *endo*-**3d** (76%) |
| 5 |  | BPSE | 6 | 25 |  *endo*-**3e** (70:30) *endo*-**4e** (overall 71%)[b] |

| | | | | | |
|---|---|---|---|---|---|
| 6 | PhCHO | Dimethyl fumarate | 17 | 70 |  *endo*-**3f** (66:34) *endo*-**4f** (overall 84%) |
| 7 |  | NMM | 17 | 70 |  *endo*-**3g** (35:65) *endo*-**4g** (overall 23%) |
| 8 |  | Dimethyl fumarate | 17 | 70 |  *endo*-**3h** (65:35) *endo*-**4h** (overall 26%) |
| 9 |  | NMM | 24 | 80 |  *endo*-**3i** (47%) |
| 10 |  | Dimethyl fumarate | 24 | 80 |  *endo*-**3j** (30%) |

[a] Isolated yield after flash chromatography.

[b] Compound *endo*-**3e** was isolated in 50% yield.

According to several NMR bidimensional experiments, especially NOESY and individual signal irradiations (Figure 2), the represented structures of the Table 1 were assigned. In the examples performed with NMM the two observed diastereoisomers could be separated. The *endo*-**4a** shown nOe between H(4)-H(5) and H(6)-H(7) but any increment of residual population was detected between H(3)-H(4) unlike to the very intense nOe observed in the case of product *endo*-**3a**. In this last molecule, nOe of H(4)-H(5) and H(6)-H(7) were also representative. In the reaction dealing with cinnamaldehyde and dimethyl fumarate the resulting pure cycloadduct *endo*-**3d** showed very intense nOe H(3)-H(4), H(4)-H(5) and H(5)-H(7) and a significant negative nOe H(6)-H(7) (see, supporting information for the analysis of NMR experiments of the other molecules).

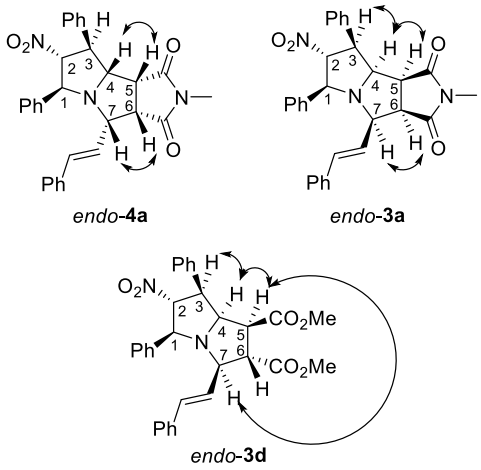
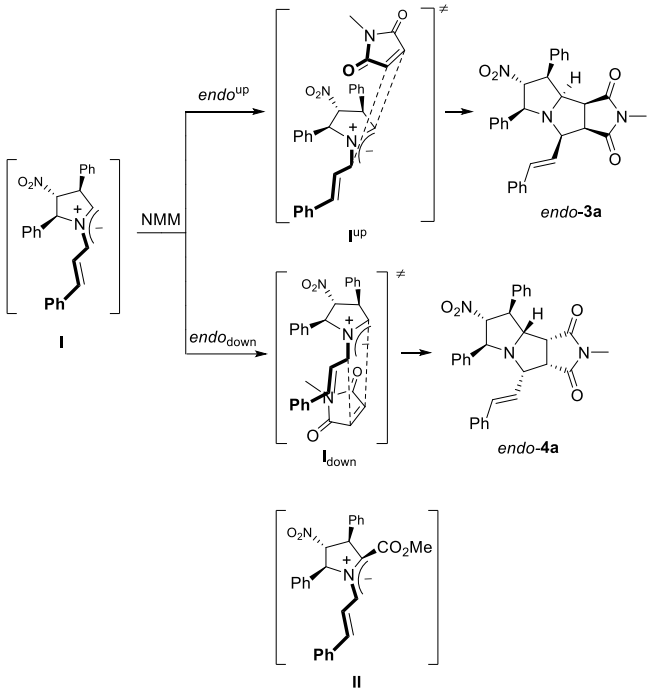



**Figure 2.** Most representative nOe in molecules *endo*-**4a**, *endo*-**3a** and *endo*-**3d**.

With all these data in hand, the absolute configuration of the resulting compounds revealed that two possible *endo*-approaches towards dipole **I** are the responsible of the reaction course, that means, the *endo*$^{up}$ and the *endo*$_{down}$ afforded cycloadducts *endo*-**3** and *endo*-**4**, respectively. For the example of NMM, the major diastereoisomer *endo*-**4a** corresponded to the *endo*$_{down}$ reaction pathway (Scheme 4). Analyzing our previous experience with the stabilized azomethine ylide **II**, the major or exclusive *endo*$_{down}$ approach occurred, through the less hindered part of the dipole [7bc], but now the absence of the methoxycarbonyl group of the pyrrolidine ring facilitated the reaction by this upper face by the NMM eluding the stereoelectronic interaction with the nitro group. In cycloadduct *endo*-**3a** the $^{1}$H NMR signal of the methyl group bonded to the nitrogen atom is shielded due to the proximity to the center of the aromatic electronic cloud (see the analogy with Figure 3 but anchoring a methyl group instead a phenyl substituent in the maleimide part). However, the methyl group in *endo*-**4a** is deshielded with respect to the corresponding one of the *endo*-**3a** around 0.5 ppm.




**Scheme 4**. Two possible endo approaches of NMM to the non-stabilized azomethine ylide **I**.

The approach of the NMM to the corresponding dipoles generated by dihydrocinnamaldehyde followed the same trend obtaining *endo*-**4g** cycloadduct as major isomer. This idea was supported by the chemical shift observed for the methyl group bonded to the nitrogen atom (see above). With phenyl-3-buten-2-one, the nature of the dipole is different and also it is much more hindered giving access to a unique diastereoisomer as a consequence of a *endo*$^{up}$ attack.

However, when the substituent of the nitrogen atom of the maleimide is an aromatic group the diastereoselection is partially displaced to a 1:1 diastereomeric *endo*-**3b**:*endo*-**4g**, mixture in the example run in the presence of NPM, or totally displaced (only one diastereoisomer *endo*-**3c** was obtained) in the case of working with *N*-(4-bromophenyl)maleimide. Using very simple calculations [28] the presence of these aromatic rings in maleimides favor a strong π-interaction between them and the phenyl ring allocated in C(3) and a very weak π-interaction with the phenyl group of the cinnamyl residue (Figure 3). It seems that the electronic inductive effect of the bromine atom increases the attraction of the two aryl moieties. The possible intense electronic repulsions of the nitro group with this bulkier maleimides is another important detail to remark.

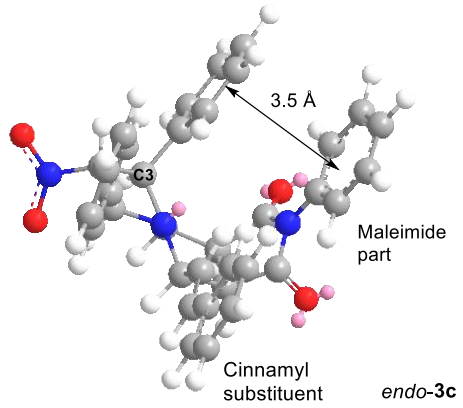



**Figure 3.** Possible π-interactions favoring the *endo*$^{up}$ approach for the reactions involving *N*-arylmaleimides.

When dimethyl fumarate was employed as dipolarophile, it was expected two possible *endo*-approaches as deduced for the behavior of NMM in Scheme 4. The exclusive diastereoisomer isolated and fully characterized *endo*-**3d**, indicated that the preference of the *endo*$^{up}$ pathway would be only possible (confirmed by nOe results depicted in Figure 2). The lower energy calculated for *endo*$^{up}$ approach also supports the presence of this unique diastereoisomer (Figure 4). These two combined data were also very interesting in order to clarify the exact position of the negative charge of the dipole **I**, which triggers the Michael-type addition (1$^{st}$ step) with simultaneous Mannich type reaction. This negative charge was better stabilized by the allylic system rather than in the inner part of the cycle matching with the stereochemical outcome observed. This model can be extended to other cycloadducts derived from dimethyl fumarate and also from BPSE.

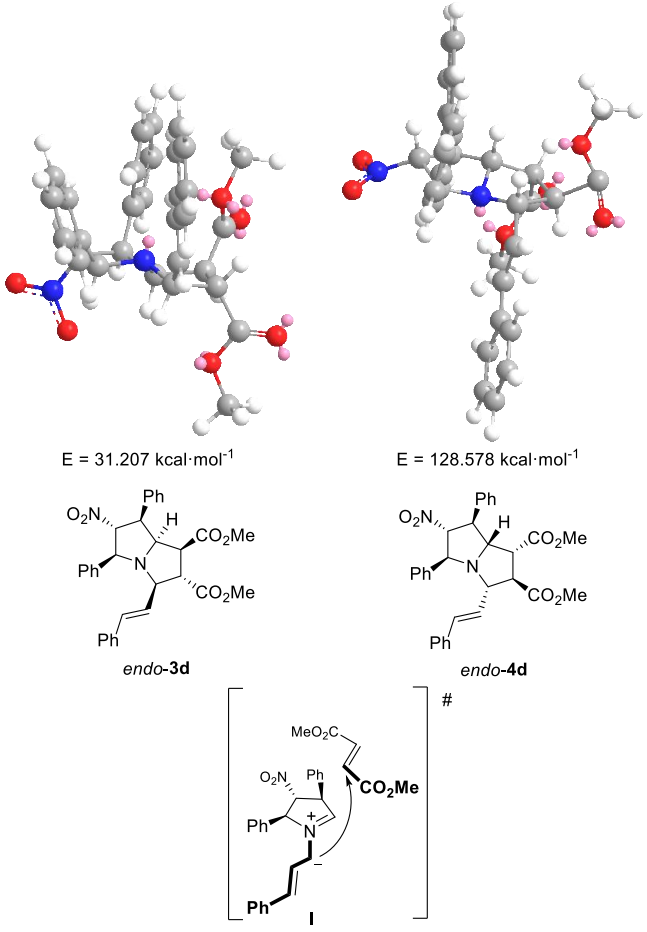



**Figure 4.** Minimun energy of *endo*-cycloadducts *endo*-**3d** and *endo*-**4d** and proposed geometry of the intermediate 1,3-dipole.

## 3. EXPERIMENTAL SECTION

### 3.1. General

### 3.2. (2*S*,3*S*,4*R*,5*S*)-4-Nitro-3,5-diphenylpyrrolidine-2-carboxylic acid, *exo*-1 [14]

To a suspension of the polisubstituted proline (400 mg, 1.23 mmol) in 5 mL of acetone was added dropwise sodium hydroxide (120 mg, 3 mmol) in 5 mL of water. The resulting mixture was stirred for 16 h. Then, the solution was cooled to 5 °C and treated with hydrochloric acid 2 M to pH 2 obtaining the desired product as a precipitate. After filtration and washing with water a yellow pale solid was afforded (326 mg, 1.04 mmol). $[\alpha]_D^{26}$ = 82.1 (c 1, acetone),[14] $[\alpha]_D^{26}$(exp.) = 61.4 (c 1, acetone); **$^1$H NMR (300 MHz, $CDCl_3$):** δ 4.54-4.66 (m, 2H, $NCHCO_2H$, NCHCHPh), 4.93 (d, J = 8.6, NCHPh), 6.46 (t, J = 8.6, $CHNO_2$) 7.28-7.68 (m, 10H, ArH) ppm.

### 3.3. General procedure for the synthesis of pyrrolizidines 3 and 4.

To a suspension of the corresponding polisubstituted proline *exo*-**1** (100 mg, 0.32 mmol) in toluene was added dropwise the corresponding aldehyde or ketone (1 equiv.). After 5 minutes was added the dipolarophile (1.1 equiv.) and the reaction mixture was checked by TLC (hexane:ethyl acetate, 8:2). The resultant solution was dried under vacuum and the crude residue was purified by column chromatography (hexane:ethyl acetate, 8:2). Time and temperatures of the different reaction are collected in the table.

#### 3.3.1 (3a*R*,4*R*,6*S*,7*R*,8*S*,8a*S*,8b*S*)-2-Methyl-7-nitro-6,8-diphenyl-4-((*E*)-styryl)hexahydropyrrolo[3,4-*a*]pirrolizine-1,3(2*H*,8b*H*)-dione, *endo*-4a

White solid (hexane/ethyl acetate). **Yield** 54%. **Melting Point:** 191-193 °C; $[\alpha]_D^{26}$ = -41.6 (*c* 1, $CHCl_3$); **IR (ATR)**: ν 1695, 1552, 1494, 1432 $cm^{-1}$. **$^1$H NMR (300 MHz, $CDCl_3$):** δ 3.04 (s, 3H, $NCH_3$), 3.34 (d, *J* = 8.2 Hz, 1H, C=CCHCHC*H*), 3.68 (dd, *J* = 10.6, 5.7 Hz, 1H, C=CCHC*H*), 4.12 (dd, *J* = 10.9, 8.6 Hz, 1H, NCHC*H*Ph), 4.24 (d, *J* = 10.9 Hz, 1H, NC*H*CHPh), 4.46 (t, *J* = 8.1 Hz, 1H, NCHC=C), 4.75 (d, *J* = 4.4 Hz, 1H, NCHPh), 5.20 (dd, *J* = 8.5, 4.5 Hz, 1H, $CHNO_2$), 6.16 (dd, *J* = 15.7, 8.0 Hz, 1H, PhCH=C*H*), 6.68 (d, *J* = 15.7 Hz, 1H, PhC*H*=CH) 7.08-7.41 (m, 15H, Ar*H*) ppm; **$^{13}$C NMR ($CDCl_3$):** $\delta_C$ 25.7 ($NCH_3$), 48.0 (C=CCHCH*C*H), 49.1 (C=CCH*C*H), 56.1 (NCH*C*HPh), 68.7 (N*C*HC=C), 70.7 (NCHPh), 73.0 (N*C*HCHPh), 102.9 ($CH_3NO_2$), 125.6 (PhCH=*C*H), 126.3, 127.2, 127.7, 128.3, 128.4, 128.9, 129.4, 129.8 (ArC), 134.8 (Ph*C*H=CH), 135.6, 136.5, 140.5 (ArC) 175.4 (NCO), 177.4 (NCO) ppm; **MS (EI):** *m/z* 493 ($M^+$-$NO_2$, 2%), 460 (12), 459 (33), 457 (16), 451 (27), 450 (100), 444 (80), 436 (33), 429 (32), 428 (69), 427 (26), 370 (12), 343 (30), 341 (59), 268 (17), 267 (13), 256 (63), 255 (79), 253 (77), 193 (80), 168 (72), 116 (20), 115 (93), 105 (69), 77 (43); **HRMS (DIP)** calcd. for $C_{30}H_{27}N_3O_4$ 493.2002, found 493.1889.

#### 3.3.2 (3a*S*,4*S*,6*S*,7*R*,8*S*,8a*R*,8b*R*)-2-Methyl-7-nitro-6,8-diphenyl-4-[(E)-styryl]hexahydropyrrolo[3,4-a]pyrrolizine-1,3(2*H*,8b*H*)-dione, *endo*-3a

Brown oil. **Yield** 36%. $[\alpha]_D^{28}$ = -23.3 (*c* 1.2, $CHCl_3$). **IR (ATR):** ν 1697, 1550, 1492, 1434 $cm^{-1}$. **$^1$H NMR (300 MHz, $CDCl_3$)**: δ 3.18 (s, 3H, $NCH_3$), 3.44 (dd, *J* = 8.3, 1.9 Hz, 1H, C=CCHCHC*H*), 3.63 (t, *J* = 8.5 Hz, 1H, C=CCHC*H*), 4.30 (m, 3H, NCHC*H*Ph, NC*H*CHPh, NC*H*C=C), 4.33-4.36 (m, 1H, NCHPh), 4.98 (t, *J* = 8.2 Hz, 1H, $CHNO_2$), 6.1 (dd, *J* = 15.8, 5.1 Hz, 1H, PhCH=C*H*), 6.68 (dd, *J* = 15.8, 1.6 Hz, 1H, PhC*H*=CH), 7.30-7.41 (m, 15H, ArH) ppm. **$^{13}$C NMR ($CDCl_3$)**: δ 15.4 (N*C*H$_3$), 49.5 (C=CCHCH*C*H), 52.2 (C=CCH*C*H), 60.51 (NCH*C*HPh), 65.6 (N*C*HC=C), 70.6 (N*C*HPh), 70.81 (N*C*HCHPh), 91.7 ($CH_3NO_2$), 127.4, 127.8, 127.9, 128.6, 129.1, 129.2, 129.5, 130.34, 132.0, 133.2, 135.0, 163.5, 169.3 (PhCH=*C*H, Ph*C*H=CH, ArC), 169.5 (CO) 179.2 (CO) ppm. **MS (EI):** *m/z* 493 ($M^+$- $NO_2$, 2%), 460 (12), 459 (33), 457 (16), 451 (27), 450 (100), 444 (80), 436 (33), 429 (32), 428 (69), 427 (26), 370 (12), 343 (30), 341 (59), 268 (17), 267 (13), 256 (63), 255 (79), 253 (77), 193 (80), 168 (72), 116 (20), 115 (100), 105 (69), 77 (43). **HRMS (DIP)** calcd. for $C_{30}H_{27}N_3O_4$ 493.2002, found 493.1889.

#### 3.3.3 (3a*R*,4*R*,6*S*,7*R*,8*S*,8a*S*,8b*S*)-7-Nitro-2,6,8-triphenyl-4-[(*E*)-styryl]hexahydropyrrolo[3,4-*a*]pyrrolizine-1,3(2*H*,8b*H*)-dione *endo-4b* and (3a*S*,4*S*,6*S*,7*R*,8*S*,8a*R*,8b*R*)-7-nitro-2,6,8-triphenyl-4-[(*E*)-styryl]hexahydropyrrolo[3,4-a]pyrrolizine-1,3(2*H*,8b*H*)-dione, *endo*-3b

Yellow oil. **Yield** 81%. **IR (ATR):** ν 1720, 1550 $cm^{-1}$. **$^1$H NMR (300 MHz, $CDCl_3$):** (1:1) mixture of diastereoisomers: δ 3.49 (dd, *J* = 8.3, 1.3 Hz, 1H), 3.58 (dd, *J* = 8.6, 1.7 Hz, 1H), 3.74 (t, *J* = 8.9 Hz, 1H), 3.83 (t, *J* = 8.3 Hz, 1H), 4.16 (dd, J = 10.6, 8.6 Hz, 1H), 4.33-4.57 (m, 6H), 4.79 (d, *J* = 4.6 hz, 1H), 5.06 (dd, *J* = 10.7, 6.7 Hz, 1H), 5.22 (dd, *J* = 8.5, 4.7 Hz, 1H), 6.11 (dd, *J* = 15.8, 4.9 Hz, 1H), 6.23 (*J* = 15.7, 7.6 Hz, 1H), 6.72 (dd, *J* = 15.8, 1.7 Hz, 1H), 6.74 (d, *J* = 15.7 Hz, 1H), 7.19-7.60 (m, 40H) ppm. **$^{13}$C NMR ($CDCl_3$):** δ 29.7, 48.3, 48.8, 50.2, 50.4, 53.8, 55.9, 65.1, 68.4, 70.5, 72.3 72.4, 73.0, 98.7, 102.5 ppm. **MS (EI):** *m/z* 510 ($M^+$, 4%), 509 (38), 450 (13), 436 (21), 378 (36), 334 (60), 329 (22), 317 (15), 316 (24), 282 (30), 258 (70), 232 (44), 190 (100), 115 (25); **HRMS (DIP)** calcd. for 555.22, found 555.22.

#### 3.3.4 (3a*R*,4*R*,6*S*,7*R*,8*S*,8a*S*,8b*S*)-2-(4-Bromophenyl)-7-nitro-6,8-diphenyl-4-[(*E*)-styryl]hexahydropyrrolo[3,4-*a*]pirrolizine-1,3(2*H*,8b*H*)-dione, *endo*-3c

Pink oil. **Yield** 80%. $[\alpha]_D^{28}$ = -92.3 (*c* 1, $CHCl_3$). **IR (ATR):** ν 2921, 2851, 1710, 1546, 1491 $cm^{-1}$. **$^1$H NMR (300 MHz, $CDCl_3$)**: δ 3.49 (dd, *J* = 8.3, 1.3 Hz, 1H, C=CCHCHC*H*), 3.85 (t, *J* = 8.3 Hz, 1H, C=CCHC*H*), 4.15 (dd, *J* = 10.5, 8.6 Hz, 1H, NCHC*H*Ph), 4.35 (d, *J* = 10.6 Hz, 1H, NC*H*CHPh), 4.56 (t, *J* = 7.7 Hz, 1H, NCHC=C), 4.78 (d, *J* = 4.7 Hz, 1H, NCHPh), 5.22 (dd, *J* = 8.5, 4.7 Hz, 1H, $CHNO_2$), 6.21 (dd, *J* = 15.7, 7.5 Hz, 1H, PhCH=C*H*), 6.74 (d, *J* = 15.7 Hz, 1H, PhC*H*=CH) 7.14-7.57 (m, 15H, ArH) ppm. **$^{13}$C NMR ($CDCl_3$):** δ 48.6 (CHPhCH*C*HCO), 49.0 (C=CHCH*C*HCO) 56.1 (NCH*C*HPh), 68.6 (C=CH*C*H), 70.9 (NCHPh), 73.2 (N*C*HCHPh), 102.5 ($CHNO_2$), 122.9 (PhCH=*C*H), 134.6 (Ph*C*H=CH), 125.2, 126.2, 127.1, 127.6, 128.1, 128.4, 128.8, 129.4, 132.6, 135.6, 136.2, 140.2 (ArC), 174.1 (N*C*O), 176.0 (N*C*O) ppm. **MS (EI):** *m/z* 586 ($M^+$-$NO_2$, 40%), 584 (37), 571 (32), 570 (98), 569 (48), 568 (93), 567 (16), 482 (23), 480 (16), 396 (15), 394 (21), 343 (24), 256 (30), 255 (32), 254 (22), 239 (17), 219 (19), 193 (64), 178 (18), 168 (67), 167 (30), 165 (16), 154 (18), 141 (17), 128 (17), 117 (30), 116 (27), 115 (100), 91 (50), 90 (24), 89 (26), 77 (43), 63 (17). **HRMS (DIP)** calcd. for $C_{36}H_{29}N_3O_4$(–$NO_2$) 586.1141, found 586.1108.

#### 3.3.5 (1*R*,2*R*,3*S*,5*S*,6*R*,7*S*,7a*R*)-Dimethyl 6-nitro-5,7-diphenyl-3-[(*E*)-styryl]hexahydro-1*H*-pyrrolizine-1,2-dicarboxylate, *endo*-3d

White solid (hexane/ethyl acetate). **Yield** 76%. **Melting Point:** 148-154. $[\alpha]_D^{26}$ = -28.3 (c 1, $CHCl_3$). **IR (ATR):** ν 1734, 1550, 1495, 1437 $cm^{-1}$. **$^1$H NMR (300 MHz, $CDCl_3$):** δ 3.49 (dd, *J* = 12.6, 10.5 Hz, 1H, C=CCHC*H*), 3.51 (s, 3H, $CO_2CH_3$), 3.66 (dd, *J* = 9.8, 7.5 Hz, 1H, C=CCHCHC*H*), 3.73 (s, 3H, $CO_2CH_3$), 4.0-4.19 (m, 2H, NCHC*H*Ph, NC*H*CHPh), 4.30 (t, *J* = 7.1 Hz, 1H, NCHC=C), 4.72 (d, *J* = 8 Hz, 1H, NCHPh), 5.16 (t, *J* = 8.6 Hz, 1H, $CHNO_2$), 6.03 (dd, *J* = 15.7, 7.4 Hz, 1H, PhCH=C*H*), 6.41 (d, *J* =

15.8 Hz, 1H, PhC*H*=CH) 7.18-7.47 (m, 15H, Ar*H*) ppm; $^{13}$C NMR ($CDCl_3$) $\delta_C$: 51.2 ($OCH_3$), 52.3 ($OCH_3$), 52.6 (NCH*C*HPh), 55.0 (C=CCH*C*H o C=CCHCHCO*C*H), 56.0 (C=CCH*C*H o C=CCHCHCO*C*H), 71.2 (N*C*HC=C), 71.5 (NCHPh), 72.6 (N*C*HCHPh), 99.9 ($CHNO_2$), 126.6, 127.3, 127.5, 127.9, 128.3, 128.5, 128.9, 128.9, 129.2, 133.0, 136.1 (Ph*C*H=CH, PhCH=*C*H, ArC), 171.2 , 172.0 (CO) ppm. **MS (EI):** *m/z* 480 ($M^+$ -$NO_2$, <2%), 376 (12), 344 (16), 194 (15), 193 (100), 178 (12), 115 (53), 105 (25). **HRMS (DIP)** calcd. for $C_{26}H_{25}N_3O_6(-NO_2)$ 480.2175, found 480.2179.

### 3.3.6 (1*S*,2*R*,3*S*,5*S*,6*R*,7*R*,7a*R*)-2-nitro-1,3-diphenyl-6,7-bis(phenylsulfonyl)-5-[(*E*)-styryl]hexahydro-1*H*-pyrrolizine, *endo*-3e

Brown oil. **Yield** 50%. $[\alpha]_D^{28}$ = 22.3 (c 1.2, $CHCl_3$). **IR (ATR):** ν 1730, 1548, 1494, 1448 cm$^{-1}$. **$^1$H NMR (300 MHz, $CDCl_3$):** δ 3.75 (m, 1H, NC*H*CHPh), 4.11 (m, 1H, CHS), 4.47 (t, *J* = 12.1 Hz, 1H, NCHC*H*Ph), 4.79 (dd, *J* = 14.4, 9.0 Hz, 1H, CHS), 5.24 (m, 1H, NCHPh), 5.47 (dd, *J* = 12.2, 8.0 Hz, 1H, $CHNO_2$), 5.81 (d, *J* = 7.4 Hz, 1H, PhCH=C*H*), 6.11 (d, *J* = 8.2 Hz, 1H, PhC*H*=CH), 7.12-7.45 (m, 25H, Ar*H*) ppm. **$^{13}$C NMR ($CDCl_3$)**: δ 46.3 (NCH*C*HPh), 48.3 ($CSO_2$Ph), 50.6 ($CSO_2$Ph), 55.5 ($CSO_2$Ph), 64.4 (NC*H*CHPh), 64.4 (C=CCH), 68.7 (NCHPh), 95.2 ($CHNO_2$), 96.16, 125.4, 126.8, 127.0, 127.1, 127.3, 127.8, 128.0, 128.6, 128.7, 128.8, 129.0, 129.0, 129.1, 129.3, 129.5, 129.6, 129.7, 129.7, 130.0 (ArC, Ph*C*H=CH, PhCH=*C*H) ppm. **MS (EI):** *m/z* 644 ($M^+$-$NO_2$, 3%), 194 (35), 193 (100), 178 (14), 168 (17), 115 (52), 91 (15). **HRMS (DIP)** calcd. for $C_{26}H_{25}N_3O_6(-C_6H_5SNO_4)$ 503.1919, found 503.1901.

### 3.3.7 (1*S*,2*S*,3*R*,5*S*,6*R*,7*S*,7a*R*)-dimethyl 6-nitro-3,5,7-triphenylhexahydro-1*H*-pyrrolizine-1,2-dicarboxylate (major), *endo*-3f

Blue oil. **Yield** 84%. **IR (ATR):** ν 1733, 1552, 1492, 1436 cm$^{-1}$. **$^1$H NMR (300 MHz, $CDCl_3$):** 64:44 mixture of diastereoisormers: δ 3.08 (s, 1.5H, $CH_3$), 3.42 (s, 1.5H, $CH_3$), 3.53 (s, 3H, $CH_3$), 3.60 (dd, *J* = 9.5, 8.4 Hz, 1H, PhCHCHCOC*H*CO), 3.69 (s, 3H, $CH_3$), 3.72 (dd, *J* = 9.6, 7.2 Hz, 1H, PhCHC*H*CO), 3.80 (dd, *J* = 11.3, 8.5 Hz, 0,5H, PHCHC*H*CO), 3.96 (t, *J* = 10.4 Hz, 0,5H, PhCHCHCOC*H*CO), 4.21 (t, *J* = 7.7 Hz, 1H, NCHC*H*Ph), 4.31 (t, *J* = 7.4 Hz, 1H, NCHC*H*Ph), 4.48 (d, *J* = 8.4 Hz, 1H, PhC*H*CHCO), 4.57-4.75 (m, 1.5H, NCHC*H*Ph, PhC*H*CHCO, NC*H*Ph), 4.71 (d, *J* = 7.6 Hz, 1H, NC*H*Ph), 4.93 (d, *J* = 10.3, 7.9 Hz, 0.5H, $CHNO_2$) 5.12 (dd, *J* = 8.9, 7.7 Hz, 1H, $CHNO_2$), 7.18-7.38 (m, 22.5H, ArH) ppm. **$^{13}$C NMR ($CDCl_3$):** δ 46.9, 49.8, 51.5, 51.9, 52.4, 52.6, 52.7, 53.4, 56.1, 57.7, 69.1, 70.0, 72.8, 73.6, 73.7, 99.7 ($CHNO_2$), 100.8 ($CHNO_2$), 125.5, 126.6, 127.1, 127.2, 127.6, 127.8, 127.9, 128.0, 128.3, 128.5, 128.6, 128.8, 129.0, 129.1, 129.3, 129.6, 135.4, 137.3, 138.9, 139.4, 140.3, 170.3 (C=O), 170.9 (C=O), 171.8 (C=O), 172.8 (C=O) ppm. **MS (EI):** *m/z* 454 ($M^+$-$NO_2$, 26%), 308 (19), 232 (20), 195 (24), 194 (15), 194 (100), 193 (16), 191 (38), 179 (20), 178 (85), 165 (23), 129 (15), 128 (17), 116 (71), 115 (94), 91 (76), 77 (21). **HRMS (DIP):** calcd. for $C_{26}H_{25}N_3O_6(-NO_2)$ 480.2018, found 454.2027.

### 3.3.8 (4*S*,6*S*,7*R*,8*S*,8a*R*)-2-Methyl-7-nitro-4-phenethyl-6,8-diphenylhexahydropyrrolo[3,4-*a*]pyrrolizine-1,3(2*H*, 8b*H*)-dione (major) *endo*-4g and (3a*R*,4*R*,6*S*,7*R*,8*S*,8a*S*,8b*S*)-2-methyl-7-nitro-4-phenethyl-6,8-diphenylhexahydro-pyrrolo[3,4-*a*]pyrrolizine-1,3(2*H*,8b*H*)-dione (minor), *endo*-3g

Yellow oil. **Yield** 23%. **IR (ATR):** ν 1728, 1536, 1489 cm$^{-1}$. **$^1$H NMR (300 MHz, $CDCl_3$):** δ (diastereoisomers mixture (1.0:0.6)): 1.73 (m, 3.2H), 2.37 (m, 1.2H), 2.70 (m, 1.6H), 2.92 (m, 0.6H), 3.02 (s, 1.3 H), 3.21 (d, *J* = 8.3 Hz, 1H), 3.39 (m, 0.6H), 3.56-3.74 (m, 3H), 4.00 (dd, *J* = , 0.6H), 4.09 (s, 0.6H), 4.24-4.33 (m, 2.2H), 4.6 (d, *J* = 5.8 Hz, 0.6H), 5.02 (dd, *J* = 8.8, 7.9 Hz, 1H), 5.10 (dd, J = 8.5, 5.8 Hz, 1H) ppm. **$^{13}$C NMR ($CDCl_3$):** δ 25.2, 25.6, 32.7, 32.8, 33.0, 37.6, 47.2, 49.7, 50.1, 53.1, 55.3, 64.3, 71.5, 72.0, 72.8, 96.7, 126.0, 126.4, 127.5, 128.0, 128.2, 128.4, 128.5, 129.1, 129.4, 129.4, 129.5, 141.1, 141.4, 177.3, 178.7 ppm. **MS (EI):** *m/z* 495 ($M^+$, 5%), 449 (33), 421 (10), 405 (20), 391 (60), 390 (80), 371 (48), 357 (41), 344 (22), 343 (43), 336 (14), 270 (15), 190 (100), 152 (45), 115 (20), 70 (12). **HRMS (DIP)** calcd. 495.22, found 495.22.

### 3.3.9 Dimethyl 2,2'-[(1*S*,2*S*,3*R*,5*S*,6*R*,7*S*,7a*S*)-6-nitro-3-phenethyl-5,7-diphenylhexahydro-1*H*-pyrrolizine-1,2-diyl]bis(2-oxoacetate) *endo*-3h (major) and dimethyl 2,2'-[(1*R*,2*R*,3*S*,5*S*,6*R*,7*S*,7a*R*)-6-nitro-3-phenethyl-5,7-diphenylhexahydro-1*H*-pyrrolizine-1,2-diyl]bis(2-oxoacetate) *endo*-4h

Pink oil. **Yield**. 26%. **IR (ATR):** ν 2832, 1731, 1533, 1494 cm$^{-1}$. **$^1$H NMR (300 MHz, $CDCl_3$):** 65:35 mixture of diastereoisomer: δ 1.62-1.82 (m, 2.6H, $CH_2$), 2.37-2.63 (m, 2.6H, $CH_2$), 3.23 (s, 1.3H) 3.34-3.37 (m, 2.2H, $CH_2CH$, $CHCO_2Me$), 3.60 (s, 3H, $CO_2Me$), 3.78 (s, 3H, $CO_2Me$), 3.76-3.80 (m, 2H, $CHCO_2Me$, NCHC*H*Ph), 4.00 (dd, *J* = 9.0, 5.2 Hz, 1H, NC*H*CHPh), 4.57 (d, J = 8.6 Hz, 1H, NC*H*CHPh), 5.04 (t, *J* = 8.6 Hz, 1H, $CHNO_2$). **$^{13}$C NMR ($CDCl_3$):** 31.6, 23.3, 33.4, 37.2, 51.6, 52.3, 52.7, 53.4, 53.7, 54.8, 65.3, 67.7, 73.2, 74.0, 74.3, 89.3, 100.3, 125.9, 127.2, 127.6,2, 127.5, 127.9, 128.0, 128.0, 128.1, 128.3, 128.4, 128.4, 129.0, 129.1, 129.2, 129.3, 129.6, 138.2, 139.1, 141.6, 171.3, 171.4, 172.3, 173.7 ppm**. MS(EI): *m/z*** 528 ($M^+$, 2%), 482 (64), 469 (12), 423 (100), 410 (32), 402 (12), 384 (10), 314 (18), 195 (21), 118 (19), 114 (64). **HRMS (DIP):** calcd. for 528.3311, found 528.3311.

### 3.3.10 (6*S*,7*R*,8*S*,8a*R*)-2,4-dimethyl-7-nitro-4-phenethyl-6,8-diphenylhexahydropyrrolo[3,4-*a*]pyrrolizine-1,3(2*H*,8b*H*)-dione, *endo*-3i

Brown oil. **Yield** 47%. $[\alpha]_D^{25}$ = 102.3 (c 1, $CHCl_3$). **IR (ATR):** ν 1733, 1551, 1494 cm$^{-1}$. **$^1$H NMR (300 MHz, $CDCl_3$):** δ 1.48 (s, 1H, $CH_3$), 3.03 (s, 3H, $NCH_3$), 3.37 (d, *J* = 8.2 Hz, 1H, CCHCO), 3.58 (t, *J* = 8.7 Hz, 1H, NCHC*H*CO), 4.35 (t, *J* = 8.5 Hz, 1H, NC*H*CHPh), 4.55 (dd, *J* = 9.0, 7.9 Hz, 1H, NCHC*H*Ph), 4.73 (d, *J* = 7.6 Hz, 1H, NCHPh), 4.95 (dd, *J* = 8.9, 7.7 Hz, 1H, $CHNO_2$) 6.19 (d, *J* = 16.1Hz, 1H, PhCH=C*H*), 6.42 (d, *J* = 16.1 Hz, 1H, PhC*H*=CH), 7.07-7.41 (15H, ArCH) ppm. **$^{13}$C NMR ($CDCl_3$):** δ 25.0 ($CH_3$), 26.5 ($CH_3$), 48.3 (CH), 51.8 (CH), 59.1 (CH), 67.4 (CH), 68.0 (CH), 71.6 (CH), 101.9 (CH), 122.8, 126.3, 126.5,

127.6, 128.0, 128.0, 128.3, 129.1, 132.7, 136.1, 138.3, 140.7 (Ar*C*, Ph*C*H=CH, PhCH=*C*H), 175.3 (CO), 176.5 (CO) ppm. **MS (EI):** *m/z* 507 ($M^{+\cdot}$ 5%), 492 (38), 461 (68), 430 (23), 404 (55), 396 (14), 359 (100), 274 (21), 193 (30), 80 (12). **HRMS (DIP):** calcd. for 507.2203, found 507.2203.

### 3.3.11 dimethyl 2,2'-((1S,2S,3R,5S,6R,7S,7aS)-3-methyl-6-nitro-5,7-diphenyl-3-((E)-styryl)hexahydro-1H-pyrrolizine-1,2-diyl)bis(2-oxoacetate), *endo*-3j

Blue oil. **Yield** 30%. $[\alpha]_D^{28}$ = 70.2 (1c, $CHCl_3$). **IR (ATR):** ν 2831, 1730, 1542, 1467 $cm^{-1}$. **$^1$H NMR (300 MHz, $CDCl_3$):** δ 1.36 (s, 3H, $CCH_3$), 3.28 (s, 3H, $CO_2CH_3$), 3.59 (s, 3H, $CO_2CH_3$), 3.65-3.74 (m, 2H, $CHCO_2Me$,$CHCO_2Me$), 3.96 (t, *J* = 10.6 Hz, NCH*CH*Ph), 4.23 (dd, *J* = 9.9, 8.3 Hz, 1H, NC*H*CHPh), 4.86 (d, *J* = 8.2 Hz, 1H, NCHPh), 5.07 (dd, *J* = 10.6, 8.2 Hz, 1H, $CHNO_2$), 6.34 (d, *J* = 16,1 Hz, 1H, CH=CH), 6.41 (d, *J* = 16,1 Hz, 1H, CH=CH), 7.23-7.44 (m, 15H, ArH) ppm. **$^{13}$C NMR ($CDCl_3$):** δ 25.5 ($CCH_3$), 49.9 (C), 52.0 ($OCH_3$), 52.4 ($OCH_3$), 58.9 NCH*C*HPh), 60.3 (*C*H$CO_2CH_3$), 60.9 (*C*H$CO_2CH_3$), 67.0 (N*C*HCHPh), 72.2 (NCHPh), 101.2 ($CHNO_2$), 126.9, 126.9, 127.6, 128.3, 128.4, 128.5, 128.9, 128.9, 129.0, 129.3, 129.6, 133.8, 135.4, 136.4, 141.0 (ArC, PhCH=*C*H, Ph*C*H=CH), 171.3 ($CO_2CH_3$), 172.2 ($CO_2CH_3$). **MS (EI):** *m/z* 596 ($M^+$, 5%), 525 (34), 495 (12), 493 (82), 350 (27), 243 (100), 220 (48), 194 (21), 193 (15), 77 (17). **HRMS (DIP):** calcd. for 593.6303, found 593.6303.

## CONCLUSION

Enantiopure *exo*-4-nitro-3,5-diphenylproline reacted satisfactorily with aldehydes or 4-phenyl-3-buten-2-one and electrophilic alkenes in a multicomponent 1,3-dipolar cycloaddition. The decarboxylation occurred at room temperature but the cycloaddition took place at different temperatures depending on the nature of the aldehyde involved. The negative charge of the dipole is located at the allylic position such as it was depicted in Figure 4. This dipole reacted by its two faces also depending of the structure of the electrophilic alkene, but always following an *endo*-approach towards the dipole. The preference of the attack is controlled by a esteroelectronic repulsion of the alkene with the nitro group and also by a possible π-interaction with the phenyl group bonded to C(3) atom. Thus, NMM attack through an $endo_{down}$ fashion except in the reaction with the unsaturated ketone, but *N*-aryl maleimides approached *via* $endo^{up}$ route. Dimethyl fumarate and BPSE both preferred the attack through the $endo^{up}$ manner.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## ACKNOWLEDGEMENTS

We gratefully acknowledge financial support from the Spanish Ministerio de Economía y Competitividad (MINECO) (projects CTQ2013-43446-P and CTQ2014-51912-REDC), the Spanish Ministerio de Economía, Industria y Competitividad, Agencia Estatal de Investigación (AEI) and Fondo Europeo de Desarrollo Regional (FEDER, EU) (projects CTQ2016-76782-P and CTQ2016-81797-REDC), the Generalitat Valenciana (PROMETEO2009/039 and PROMETEOII/2014/ 017) and the University of Alicante.

## SUPPLEMENTARY MATERIAL

Copies of 1H and 13C NMR spectra and, their corresponding NOESY-nOe are supplied as Supportive/Supplementary Material.

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